uronic acid units, wherein the uronic acid units are selected from the group consisting of D-glucuronic acid and L-iduronic acid and $-O-SO_3$ groups are positioned at any but not all of carbons 3 and 6 of the D-glucosamine units and carbons 2 and 3 of the uronic acid units and further wherein linkages between D-glucosamine and uronic acid are of the 1-4 alpha type, and linkages between L-iduronic acid and D-glucosamine are of the 1-4 alpha type, and linkages between D-glucuronic acid and D-glucosamine are of the 1-4 beta type.--

REMARKS

Entry of this preliminary amendment is respectfully requested before action is taken in this case.

Claims 106-107, 141-199 are now in this case. Claims 141-199 have been added. Claims 42-48, 85-105, 108-140 have been cancelled.

Attached is a table generally describing the added claims and setting out examples of where support can be found in the specification for them. This table is intended as an aid for the examiner. It is not intended to indicate where all support may be found, but only, to give examples of where support may be found.

An interview was held with Examiner Rollins on November 13, 1987 at 10:00 a.m. Present at the interview were: Seth Jacobs, Chantal Peaucelle and the examiner.

The following is a summary of what was discussed at the interview:

Heparin is a compound in widespread use as an anticoagulant. Heparin is found in natural tissues as a mixture of oligosaccharides. The oligosaccharides are comprised of alternating D-glucosamine and uronic acid residues (the uronic acid being either D-glucuronic acid or L-iduronic acid). These residues are linked in a stereospecific manner (alpha or beta) between carbons one and four. The oligosaccharides in natural heparin are of different lengths, and a given length will exist in several forms having different sulfation patterns. The different sulfation patterns can cause oligosaccharides of the same length to have different ionic strengths. Oligossacharides of the same length but having different sulfation patterns can have different properties.

Commercial heparin has been derived from natural heparin and therefore it has consisted of mixtures of chains. These mixtures are heterogeneous in that they consist of different lengths of saccharides, and each length of saccharide exists as a mixture of different sulfation patterns. Even if chains are isolated from natural sources which have the same length, those chains would have different sulfation patterns. The chains would not be of the same structure and thus would be in an impure mixture.

There has been no practical way to obtain pure heparin chains which have the same length and the same sulfation pattern. Therefore it has not been possible to effectively study properties

of chains having selected sulfation patterns. Nor has it been possible to quantitatively prepare these chains.

Applicants have discovered a means of synthetically producing heparinic compounds. Their discovery has been hailed as a milestone in the art and has opened up a broad new field centered around the products and processes of this invention. Their claimed invention allows the synthesis of heparin chains in a tailor made way to obtain substantially pure chains of the same structure, i.e. chains having the same length, and the same sulfation pattern. In other words, the invention allows custom tailoring of heparin chains of a given length. This invention has enabled the inventors to discover a pentasaccharide, as in claim 106, which has a certain sulfation pattern which endows the compound with a surprising activity (Yin Wessler activity of over 2,000). The invention claimed allows the preparation of heparinic chains in any quantity desired and thus allows the chains to be used as drugs and as research tools.

The invention claimed consists of processes for synthesizing heparin and heparinlike chains, and products of these processes. The processes claimed include condensing saccharides together to form a protected condensation product which has protecting groups that allow selective positioning of functional groups such as sulfate; elongating the protected condensation product; and - positioning functional groups, such as sulfate, on a heparinic polysaccharide. The products claimed include final products and intermediates of these processes.

As stated above, the invention of this application has been recognized as a pioneering step which has opened up a broad new field centered around the processes and compounds of the invention.

The attached article by Casu in Advances in Carbohydrate Chemistry and Biochemistry, Vol. 43, 1985, refers to this invention a "milestone".

In 1986, the prestigious Galien Prize was shared by three of the inventors for the work leading to this invention. The Galien prize is awarded for the most outstanding achievement of the year in drug research. The previous year the Galien Prize was awarded to Luc Montagnier for the discovery of the AIDS virus.

One of the inventors, Maurice Petitou, has received The French Carbohydrate Group Award for his work on this invention. The French Carbohydrate Group Award is awarded for poineering original work in the carbohydrate industry. A copy of the award certificate is enclosed.

Mr. Petitou has also been invited to draft a chapter on the chemical synthesis of heparin in a book entitled "Heparin". This book is still in press and is edited by Lindahl and Lane. An article by Lindahl has been cited by the examiner in this application.

In addition, the inventors have been invited to lecture widely on this invention to others scientists working in this

field. A copy of a presentation by inventor Choay to the New York Academy of Sciences on November 3-5, 1987 is attached.

Furthermore, there has been a large demand by other scientist for samples of compounds of the invention.

Finally, EPO patent which is equivalent to this application has been granted with broad claims covering products and processes.

In arriving at the claimed invention, the inventors had to overcome many problems. Inventor Petitou was told by one of the authors of one of the cited references in this case, Lindahl, that synthesizing the saccharides of the invention was not possible.

The inventors had to discover whether the carbon 4 of the uronic acid would react to form a 1-4 linkage with the carbon 1 of a D-glucosamine. It was not known whether the carbon 4 the uronic acid was reactive. In addition, they also had to discover whether the linkage obtained could be an alpha linkage as in heparin.

In addition, L-iduronic acid (one of the two uronic acids in heparin) had not been much studied up until that point. One reason for this was that the methods known for making iduronic acid were not very quantitative. Another reason was that there was no method known for positioning functional groups such as sulfate on L-iduronic acid at positions corresponding to those of heparin type oligosaccharides. The inventors discovered a new

method for synthesizing iduronic acid, which method is the subject of co-pending application Ser. No. 453,731.

Once the initial condensation had been performed, the inventors had to discover a means of employing protecting groups which could be removed after the condensation in order to elongate the saccharide to reach the desired saccharide length.

The inventors also had to discover a pattern of protecting groups which would allow functional groups, in particular sulfate, to be positioned at any desired carbon position after the condensation or elongation had occurred.

The protecting groups involved in this invention are:

A. Semi-permanent protecting groups;

B. Permanent protecting groups;

C. Protecting group which form an ester at carboxyl groups;

D. Temporary protecting groups; and

E. "Inert" protecting groups.

Each of these protecting groups had to be removable at the right time without disturbing the remaining protecting groups. They also had to be compatible with stereochemistry of the reaction. They also had to be stable during the condensation. They also had to be removable in the presence of functional groups which had been added on to the saccharide.

The inventors solved these problems in part by using a method which the art taught against. Specifically, the inventors removed benzyl permanent protecting groups in the presence of

sulfate functional groups even though in Turvey, J. Chem. Soc., 1962 (see supplemental amendment in Ser. No. 457,931 mailed March 6, 1987) it was taught that this sequence of steps was impractical in that a low yield would be obtained, and only after several repetitions. Contrary to the teaching of Turvey, the inventors have obtained a good yield using this sequence of steps.

After the above remarks were presented to the examiner at the interview of November 12, the examiner stated that there was no need to distinguish the claimed invention over the art cited. The above remarks are believed to be sufficient to distinguish applicants' invention over the cited art.

Other applications by the inventors are pending which concern related inventions.

Application Ser. No. 856,855 relates to a synthesis involving D-galactosamine and uronic acid.

Application Ser. No. 888,527 relates to a process for synthesizing particular heparinic disaccharides.

Application Ser. No. 734,445 relates to heparinic tetrasaccharides discovered by the inventors.

Application Ser. No. 453,731 relates to the preparation of the starting saccharides used in this process.

During the interview it was pointed out to the examiner that claim 41 was indicated allowed in the actions of Feb. 14, 1985, and Sept. 17, 1985. Then in the action of June 25, 1986, claim 41 was indicated to be rejected on the summary sheet while there was no discussion of the rejection in the body of the action.

Examiner Rollins indicated that the prior examiner may have inadvertently rejected claim 41. Claim 41 was subsequently cancelled, and claim 106 substituted for it. Claim 106 is presently in the action, as is claim 107, which claims the pentasaccharide as a pharmaceutical. Applicant respectfully requests allowance of these claims on the grounds that cancelled claim 41 was inadvertantly rejected.

During the interview, sample process claims were shown to the examiner. These claims have been revised and new claims added. The examiner indicated that he wished to review the claims for support in the specification. To aid the examiner in this, applicants have provided a table (attached) which provides a general description of the claims and lists some examples of where support for them can be found in the specification.

Applicants would like to thank the examiner for the curtesy extended by him during the interview to applicants' U.S. patent attorney, Seth Jacobs, and to applicants' French agent, Chantal Peaucelle.

Allowance of this application is respectfully requested on the basis of the new claims presented and the remarks made in this amendment.

Applicants would welcome a phone call from the examiner to discuss the claims presented here, or any other aspect of the amendment.

Respectfully submitted,

By _____

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